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IDSA
Infectious Diseases Society of America

January 5, 2015

Representative Fred Upton
2183 Rayburn House Office Building
Washington, DC 20515

Representative Diana DeGette
2368 Rayburn House Office Building
Washington, DC 20515

Submitted electronically to cures@mail.house.gov

RE: 21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests

Dear Chairman Upton and Representative DeGette:

The Infectious Diseases Society of America (IDSA) thanks the Committee for this opportunity to comment on the 21st Century Cures request for feedback, "A Modernized Framework for Innovative Diagnostic Tests." IDSA welcomes the Committee's interest in the recently released FDA framework for regulating laboratory developed tests (LDTs) as well as the Committee's broader commitment to incentivizing the development and clinical integration of innovative diagnostic tests.

IDSA recognizes that there are valid concerns about the risks associated with LDTs in areas such as cancer, genetic testing, as well as infectious diseases. While many infectious disease (ID) LDTs have a long history of safe and effective use in patient care, other ID LDTs may not have been evaluated as rigorously. Nonetheless, IDSA believes the risks raised by the use of ID LDTs are dwarfed by their advances and benefits to patient care. Unlike other disease areas, the evidence that the ID LDTs provide unreliable results that lead to harmful patient care decisions is lacking.

IDSA is very concerned that LDT oversight, as currently proposed by the Food and Drug Administration (FDA), could impede patient access to existing high quality or state of the art tests and may curtail the development of novel tests for emerging infectious diseases. We are pleased to offer recommendations to help ensure that appropriate patient access to ID LDTs is maintained, and we will also share these recommendations with the FDA at the agency's January workshop on this topic as well as in a formal comment letter. We look forward to continuing to work with the Committee on these important issues.

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii, Klebsiella pneumoni*ae, and *Pseudomonas aeruginosa*, and, finally, emerging infections such Ebola virus, enterovirus D68, Middle East Respiratory Syndrome Coronavirus

(MERS-CoV), and bacteria producing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.

Over the past several years, IDSA has stressed the importance of innovative diagnostic devices for the care of patients suffering from infectious diseases, most notably in our 2013 report, Better Tests, Better Care: Improved Diagnostics for Infectious Diseases. Improved diagnostics can allow physicians to rapidly identify the pathogen infecting a patient and prescribe the most appropriate treatment, increasing the likelihood of a positive patient outcome. Notably, high quality ID diagnostics have a unique ability to protect the broader public health by alerting health officials of the need to trigger protocols to contain outbreaks and prevent the transmission of infections. Below IDSA is pleased to respond to key questions posed by the Committee:

3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?

Multiple factors may be considered when defining risk. IDSA recommends that the FDA consider past and present uses of LDTs, recognize different patterns of use in different disease areas, and document both harm and benefits that LDTs contribute to patient care. The FDA should balance the risk associated with current use of LDTs in each relevant disease area against the risk of curtailing patient access to LDTs under the proposed regulations. While many ID LDTs have a long history of safe and effective use in patient care, other ID LDTs may not have been evaluated as rigorously. Nonetheless, IDSA believes the risks raised by the use of ID LDTs are dwarfed by their advances and benefits to patient care.

In its regulatory framework, the FDA has prioritized oversight of high risk LDTs for "certain infectious diseases with high-risk intended uses," notably viral load tests for cytomegalovirus. These LDTs have been in use for many years by laboratories, with well-documented data demonstrating clinical validity and peer reviewed literature supporting their use. In many instances, these LDTs have become the standard of care. Given their longstanding use and significant supporting data, **IDSA asserts that tests for transplantation-related viruses do not pose a high risk to patients and should be reclassified as moderate risk tests. IDSA offers the expertise of its members to assist in this process.**

5. Are there areas where the balance between pre-market review versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

Earlier in 2014, FDA issued a pair of guidance documents on this issue, entitled, "Expedited Access for Premarket Approval of Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions," and "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval." IDSA applauded these guidances for taking steps to speed patient access to urgently needed diagnostic tests, and **we recommend that FDA extend this level of flexibility to LDTs that it intends to regulate.**

For medical devices addressing unmet medical needs, greater uncertainty about the benefit-risk profile of the device should be accepted and by shifting data collection from the pre-market to post-market phase, urgently needed life-saving devices can reach patients more rapidly. For a patient with a serious or life-threatening infection that cannot be identified in a sufficiently rapid manner to substantively impact care and outcomes, FDA must appropriately weigh the risk of approving a new diagnostic test based upon a smaller premarket data set against the risk of not having urgently needed new diagnostics.

There are several important infectious disease areas for which it is extremely challenging to collect large quantities of pre-market data due to the rare occurrence of certain diseases, such as viral encephalitis or invasive fungal infections. This challenge can hamper the development of both commercial diagnostics and LDTs. In such instances, allowing approval of tests based upon smaller premarket data sets and facilitating collection of postmarket data can allow urgently needed tests to reach patients while the utility of using these tests continues to be studied in clinical settings.

6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?

When manufacturers make improvements to tests, the process that has been created to speed the clearance of the modified test is extremely important to improving access to testing. For example, when adding an emerging pathogen to a multiplexed test, it is expected that a comprehensive analytical validation will be completed. **Allowing a more limited clinical trial to be performed focusing on the new pathogen would make the test available to clinical laboratories in a more rapid manner.** Given how rapidly pathogens emerge and evolve, lack of frequent updates is particularly problematic in the area of infectious diseases and a key factor in the need for continued flexibility in this disease area.

Finally, the FDA has indicated that if a commercial test is used on a specimen other than what was originally intended, that test would be considered an LDT subject to oversight. **IDSA argues the need to test these non-intended specimens represent an unmet medical need.** For example, if a commercial diagnostic can identify a given pathogen in serum, but there exists a need to test cerebrospinal fluid (CSF) for the same pathogen, the use of an analytically verified LDT to test CSF for this pathogen should be subject to oversight discretion.

9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g. Ebola)?

The FDA currently use the Humanitarian Use Devices (HUD)/Humanitarian Device Exemption (HDE) to define diagnostics for rare diseases as those for which no more than 4000 tests are performed each year nation-wide. Rare infectious diseases present some unique challenges to the FDA's current definition. Rare infections, such as encephalitis caused by herpes simplex virus (HSV) and varicella zoster virus (VZV), or invasive aspergillosis have symptoms that are

also common in more widespread infections. In order for these rare infections to be ruled out, they must be tested for at far higher rates than the FDA limit of 4000/year nationwide.

The Center for Drug Evaluation and Research (CDER) at the FDA defines rare diseases, based on the 1983 Orphan Drug Act, as those that affect less than 200,000 patients nationwide. **IDSA proposes that the LDT regulatory framework align with this definition to permit oversight discretion for LDTs for diseases with less than 200,000 patients in the United States.** In addition, pathogens can cause both common and rare diseases; for example, herpes encephalitis is a rare disease, while genital herpes infection and fever blisters are much more common. **IDSA recommends that the FDA not constrain its definition of a rare disease based on the pathogen, but rather on the disease itself.**

For LDTs that address unmet medical needs, IDSA has concerns over the regulatory framework the FDA has proposed when a commercial test meeting this need is approved. **IDSA does not believe the 12-month period laboratories are given to submit to the FDA or switch to the commercial test is sufficient, and recommends at least a 2-year phase-in period.** Most clinical microbiology laboratories operate under a 12-month capital upgrade cycle, and depending on when a commercial test is approved, would not likely be able to purchase the equipment needed for a test within the 12-month period, resulting in situations where laboratories may lose the capability to conduct any testing for critical unmet medical needs.

IDSA also urges the FDA to delay regulatory oversight of LDTs for unmet medical needs until several commercial tests are approved. With only one option, laboratories may be forced to purchase expensive equipment that may be used for only one test. Delaying regulatory oversight of LDTs for unmet medical needs until several commercial tests for the unmet medical need are approved will give laboratories much needed flexibility to choose tests appropriate to their space and cost limitations. Moreover, while the vast majority of FDA-approved and cleared tests have excellent performance characteristics, there are clear instances of tests that identify viral resistance mutations in which LDTs have superior performance characteristics compared to commercial tests. Delaying enforcement until multiple commercial tests are approved will assist laboratories in addressing these issues.

11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?

IDSA proposes several policies to directly support the development of new diagnostic tests as well as to encourage their appropriate use, which benefits patient care and helps ensure a market for these products. Below is an overview of policies IDSA believes could be incorporated into the 21st Century Cures initiative, which we also discussed in our May 30 letter to the Committee in response to the first 21st Century Cures white paper.

Public Private Partnerships: **Direct the Department of Health and Human Services (HHS) to establish a public private partnership (PPP) similar to the European Rapid Point-of-Care test Platforms for Infectious Diseases (RAPP-ID) program and to include diagnostics in the new biopharmaceutical incubator announced as part of the National Strategy for Combating Antibiotic Resistant Bacterial (CARB).** In 2011, the European Commission (EC) launched RAPP-ID, a PPP bringing together government experts, academia and industry aimed

at developing fast and reliable point-of-care tests for the detection of various pathogens. In the U.S., Biomedical Advanced Research Development Authority (BARDA) currently partners with companies on diagnostic R&D, but BARDA does not currently bring together multiple companies with government and academic experts to collaborate and share information.

Biorepositories: **Direct the National Institute for Allergy and Infectious Diseases (NIAID) to examine opportunities to support the development of virtual biorepositories for viruses, fungi and other pathogens, utilizing samples already being collected for research, similar to the existing bacteria virtual biorepository. Provide incentives and support for institutions to save de-identified specimens and to participate in virtual biorepository catalogues.** A key challenge in clinical trials for new diagnostics is access to clinical samples, particularly those containing rare pathogens. The Antibacterial Resistance Leadership Group (ARLG), a research team funded by NIAID, established a Virtual Biorepository (VB) Catalogue, a searchable, web-based system that provides researchers with unique access to clinically well-characterized bacteria for the development of diagnostic tests and other research. The bacteria are housed at multiple locations. This approach requires significantly less resources than traditional physically centralized biorepositories.

Conflict of Interest: **Clarify that institutions receiving federal funding should implement conflict of interest (COI) policies that appropriately enable transparent industry/institutional research collaborations.** Often expert input or independent validation of a potential test is needed during development. Institutional COI policies are often much more strict than the National Institutes of Health (NIH) COI regulatory framework, which was intended to provide guidance to institutions on how to manage COI. Unfortunately, institutional COI policies often bar those best suited for these activities, sometimes even if the expert is willing to work for free on his or her own time. This forces developers to forgo expert input or use laboratories lacking expertise for independent testing. This loss of expert input and the resources diverted to train and supervise testing at labs lacking expertise can add considerable time and cost to diagnostic development.

Physician education programs on the utility of new diagnostics: **Direct the Agency for Healthcare Research and Quality (AHRQ), specifically through its Center for Evidence and Practice Improvement (CEPI), to conduct or support research to demonstrate the impact of new ID diagnostics on patient care and outcomes, and to disseminate the results of that research to physicians to encourage them to appropriately utilize new diagnostics.** Many physicians and other health care providers may be hesitant to use new diagnostic tests, in part because they are often uncertain of how best to integrate them in their practice and how to interpret results. Little guidance currently exists on the use of diagnostic tests for a particular type of infection, or what bundles of tests should be used if a patient has a particular set of symptoms. The ability to construct useful guidelines is hampered by the lack of clearly designed outcomes studies demonstrating patient benefit when tests are used as part of clinical decision making. CEPI is well-suited to address this need, as the Center is tasked with conducting and supporting research on health care delivery and improvement and advancing decision and communication sciences to facilitate informed treatment and health care decision making by patients and their health care providers.

Again, IDSA thanks you for opportunity to provide comments on this important topic. Should you have any additional questions, please contact Jonathan Nurse, IDSA's Director of Government Relations, at jnurse@idsociety.org or 703-299-0202.

Sincerely,

[redacted]

Stephen B. Calderwood, MD, FIDSA
IDSA President

Ovarian Cancer
NATIONAL ALLIANCE
We Work To Save Women's Lives

January 5, 2015

The Honorable Fred Upton
Co-Chair
21st Century Cures Initiative
Chairman
Committee on Energy and Commerce
United States House of Representatives

The Honorable Diana DeGette
Co-Chair
21st Century Cures Initiative
Committee on Energy and Commerce
United States House of Representatives

Dear Chairman Upton and Congresswoman DeGette:

The Ovarian Cancer National Alliance (hereafter, the Alliance) thanks you for the opportunity to comment upon the white paper "A Modernized Framework for Innovative Diagnostic Tests." The Alliance is a powerful voice for everyone touched by ovarian cancer. We connect survivors, women at risk, caregivers and health providers with the information and resources they need. We advocate at a national level for greater investment in federal research to support the development of an early detection test, improved health care practices and life-saving treatments – goals shared with those of the 21st Century Cures Initiative. We appreciate your attention to the important issue of regulation of Laboratory Developed Tests (LDTs) and look forward to sharing the ovarian cancer community's perspectives, concerns and priorities.

In September 2014, the House Energy and Commerce committee held a hearing regarding the regulation of LDTs and the draft proposal by the Food and Drug Administration (FDA) to do so. At that time, we submitted comments to the committee, dated September 9, 2014, emphasizing the ovarian cancer community's robust support for FDA's actions[1]. Following the release of a deeply flawed LDT (OvaSure, which purported to be an early detection test for ovarian cancer), our community has long called for greater oversight of LDTs to ensure that they are valid, reliable, safe and effective.

The Alliance is united with many other patient advocacy groups, professional societies and academic researchers in support of FDA's draft guidance outlining a path for oversight of LDTs[2]. We believe that the regulatory paradigm laid out by the FDA allows for continued innovation, yet also ensures robust patient protections by providing that all molecular diagnostics – whether they are LDTs or distributed as kits by a manufacturer – are validated to ensure they are reliable, reproducible, safe and effective. Indeed, we recently applauded the decision by the FDA to approve Myriad's LDT for *BRCA* testing (BRACAnalysis) as a companion diagnostic for the new ovarian cancer drug, Lynparza[3]. Through this approval, Myriad demonstrated that it is possible for an LDT to undergo accelerated FDA review and be approved in a timely and efficient manner. Furthermore, many of the IVDs used in ovarian cancer diagnosis and recurrence monitoring (*e.g.* OVA1, CA-125, HE-4) have gone through the FDA clearance process, again emphasizing the feasibility of the FDA review.

We believe many of the questions from the white paper have been answered fully or in part by the FDA's draft guidance document and will be discussed in great detail at the agency's public meeting January 8-9, 2015. We look forward to the discussion at that meeting and believe it will serve to guide FDA as it reviews, and hopefully, finalizes this guidance. To the extent that the questions outlined in the 21st Century Cures white paper are not addressed by the FDA's guidance, we will seek to answer those remaining questions below.

[1] Our letter, which details the OvaSure case and how FDA regulation would have prevented the test from harming women, is enclosed here for your convenience.
[2] December 10, 2014. AIDS Institute et al., Letter to Public Docket FDA-2011-D-0360. (Enclosed)
[3] December 19, 2014. Food and Drug Administration. FDA Approves Lynparza to treat advanced ovarian cancer. Available at: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm427554.htm

The white paper requests comment on a number of ways in which LDTs may differ from other in vitro diagnostics (IVDs) manufactured as test kits, such as risk classification, pre-market and post-market review, and labeling. From the patient perspective, there is no distinction between an LDT and an IVD kit; in fact, most patients and their providers will not know which type of test they are ordering nor which type was actually performed by a laboratory. All tests are ordered, interpreted, and reported to a provider in an identical manner, and therefore should be subject to the same regulatory oversight – including risk classification, pre-and post-market review standards, and labeling.

The white paper also requests comment on where the lines should be drawn between interpreting patient test results and the practice of medicine, regarding IVDs. It has been well documented that health care providers do not have the education or time necessary to stay up-to-date on the latest advances in diagnostics[4]; however, patients require accurate ordering, completion and interpretation of tests for their care. All IVDs, regardless of whether they are test kits or LDTs, should be reported to the ordering provider with enough information and interpretation to guide evidence-based medical decision making. Furthermore, there should be clear and established lines of communication between laboratories and providers to allow for accurate ordering, decision support and adverse event reporting.

Another area the white paper asks for comment on is whether current diagnostics should be "grandfathered" into the current marketplace. We urge the committee to not pursue this idea – the FDA guidance outlines a thoughtful pathway for reviewing old tests in a risk-based fashion over a 9 year time frame, while leaving tests on the market as they await review. This process will ensure that bad tests are found and removed from the marketplace and levels the playing field for those developing new diagnostics, which will have to undergo review.

Finally, the white papers asks what incentives can be put in place to encourage the development of novel diagnostics. FDA oversight is not at odds with the development of new diagnostics; indeed, many of the tests currently used in the diagnosis, monitoring and treatment of ovarian cancer have gone through the FDA approval process[5]. What is at odds with the development of new diagnostics is regulatory uncertainty. Allowing the FDA guidance to move through the public comment period into final guidance will provide regulatory clarity to test developers and venture capital firms, ushering in more investment and innovation in the diagnostics we need to conquer diseases like ovarian cancer.

Sincerely,

Calaneet H. Balas
Chief Executive Officer
Ovarian Cancer National Alliance

Enclosure:

- September 9, 2014. Ovarian Cancer National Alliance. Statement for the Record re: "21st Century Cures: Examining the Regulation of Laboratory Developed Tests" hearing.
- December 10, 2014. AIDS Institute, et al. Sign-on letter in support of FDA moving forward with LDT regulation. Public Docket FDA-2011-D-0360.

[4] Grey et al. 2014. Physicians' Attitudes About Multiplex Tumor Genomic Testing. *JCO*. 32: 1317-1323.
[5] Abbott's CA-125, Vermillion's Ova1, Quest's HE-4 and Myriad's BRACAnalysis have all gone through FDA review.

Ovarian Cancer National Alliance

Statement for the Record

U.S. House Energy & Commerce Committee

Subcommittee on Health

Hearing: "21st Century Cures: Examining the Regulation of Laboratory Developed Tests"

September 9, 2014

The Ovarian Cancer National Alliance (hereafter the Alliance) would like to thank Chairman Pitts, Ranking Member Pallone and Members of the Subcommittee for the opportunity to comment upon the recent hearing regarding the regulation of laboratory developed tests (LDTs). The Ovarian Cancer National Alliance is a powerful voice for everyone touched by ovarian cancer. We connect survivors, women at risk, caregivers and health providers with the information and resources they need. We advocate at a national level for greater investment in federal research to support the development of an early detection test, improved health care practices and life-saving treatments.

During the hearing, we were pleased to hear so many Members of the Subcommittee call for stronger oversight of LDTs, even if there was disagreement on which agency should carry out that oversight. Ensuring that LDTs are valid, reliable, safe and effective is of critical importance to the ovarian cancer community, as we have experienced firsthand the harmful repercussions of an unregulated LDT. As we also heard many Members ask for examples of harmful LDTs, we submit this letter to detail our community's experience with OvaSure, a harmful LDT pulled from the market in 2008.

OvaSure – A Case Study Highlighting the Need for LDT Regulation

Ovarian cancer is a highly deadly disease, taking the lives of nearly 14,000 women in the United States each year. A full quarter of women diagnosed with ovarian cancer will survive less than one year, and over half won't live five years past diagnosis. These grim statistics are due to the fact that there is no early detection test for ovarian cancer – though the need is obviously great. Most cases of ovarian

cancer are caught only after the disease is in its most advanced stages and difficult to effectively treat. However, when the disease is caught early, it can be treated effectively through surgery and chemotherapy.

It is against this backdrop that, in 2008, Labcorp began marketing an LDT called OvaSure as an early detection test for ovarian cancer. The test had been developed by Dr. Gil Mor at Yale University and was quickly commercialized by the testing company, before it had been sufficiently validated.

Almost immediately upon commercialization, the Food and Drug Administration (FDA)[1] and the Society of Gynecologic Oncology[2,3] stated that they did not believe the test had been validated enough for routine clinical use. Furthermore, it was reported that women using the test had experienced false positives[4] and false negatives[5] – leading otherwise healthy women to unnecessarily have their ovaries removed and leaving some women with a false sense of security after missing their cancer diagnosis. Both of these outcomes put women at exceptional and unnecessary risk.

The OvaSure test was eventually pulled after four months on the market[6]. Since laboratories offering LDTs are not required under the Clinical Laboratory Improvements Act (CLIA) to report adverse events, we do not know precisely how many women were harmed by the OvaSure test, but we do know that the test should have never been on the market to begin with.

FDA Regulation of LDTs Will Prevent the Next OvaSure

The Alliance applauds FDA's recent steps towards ensuring that all molecular diagnostic and genetic tests are validated to certify that they are reliable, safe and effective. We welcome the development and use of tests that can help guide treatment for women with and at risk of developing ovarian cancer, but we must first have confidence that these tests are valid. FDA regulation of LDTs will ensure that.

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[1] August 7, 2008. OvaSure Manufacturer Letter from the Food and Drug Administration to LabCorp. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm125130.htm

[2] On April 4, 2012, the Society of Gynecologic Oncologists changed its name to the Society of Gynecologic Oncology. All references to the organization in this letter will use its current name.

[3] July 2, 2008. Society of Gynecologic Oncology Statement Regarding OvaSure. Available at: https://www.sgo.org/wp-content/uploads/2012/09/Statement-On-Ovasure.pdf

[4] August 25, 2008. Andrew Pollack. "Cancer Test for Women Raises Hope, and Concern." New York Times. Available at: http://www.nytimes.com/2008/08/26/health/26ovar.html?pagewanted=1&_r=0

[5] March 23, 2011. Lizzie Buchen. "Cancer: Missing the mark." Nature. Available at: http://www.nature.com/news/2011/110323/full/471428a.html

[6] October 24, 2008. Andrew Pollack. "Sales of Test for Ovarian Cancer Halted." New York Times. Available at: http://www.nytimes.com/2008/10/25/business/25cancer.html

We deeply appreciate and support several facets of FDA's proposed regulatory framework for LDTs:

- *Risk Based Framework:* FDA proposes a phased-in, risk-based framework to regulate LDTs. In short, FDA will classify LDTs by their risk level and phase in review of those tests by prioritizing the highest risk tests. Tests will be classified as high risk if they are used as the basis of any high risk medical decision, such as picking a chemotherapy, diagnosing a disease in asymptomatic individuals and evaluating blood and blood products for use in humans. This will include any companion diagnostic tests or an LDT that mimics a companion diagnostic currently on the market. It is likely that many of the tests relevant to the ovarian cancer community will count as class III tests (e.g. BRCA testing for chemotherapy selection or prophylactic surgery, early detection tests and tests to monitor disease recurrence). Under the risk based framework, tests currently on the market will remain on the market while they are awaiting review, though all new tests must be reviewed prior to being offered. Had this framework been in effect in 2008, OvaSure would have been required to undergo FDA review for analytical and clinical validity prior to being put on the market. OvaSure's substantial flaws would have been identified through this process and it would have been identified through this process, and patients and providers would have been spared the adverse consequences of an inaccurate, unreliable test.

- *Adverse Event Reporting:* Within six months of the finalization of FDA's guidance, laboratories will be required to report all adverse events resulting from the use of their tests to the FDA. Using the example of OvaSure, events such as the misdiagnosis of ovarian cancer in healthy women (false positives) or missing ovarian cancer recurrence (false negatives) would be reported to the FDA. Had this oversight been in place in 2008, we would have an accurate count of the number of women harmed by the OvaSure test.

Furthermore, we believe that FDA's action to end enforcement discretion with regard to LDTs will provide clarity and peace of mind to patients, providers and payers. As LDTs are increasingly being used to guide complex medical treatment decisions, it is critical that when patients and their doctors use such a test, they know the results can be trusted. Payers will also be able to better assess the benefit and value of a test, allowing them to decide if a test should be covered, for which patients, and at what reimbursement rate.

The Impact of FDA Regulation of LDTs on Ovarian Cancer Patients

Under FDA's proposed framework to regulate LDTs, ovarian cancer patients will continue to have access to all the diagnostics currently used in their care. There are currently two main classes of diagnostics being used by ovarian cancer patients and their providers and we will summarize each below:

- *Tests to diagnose suspected ovarian cancer and monitor disease recurrence:* There are currently three molecular diagnostic tests on the market used to either diagnose ovarian cancer when it is suspected or to monitor disease recurrence in survivors. These three tests – CA-125, HE-4 and OVA-1 – have all gone through the premarket review process and been cleared by the FDA. Their status will not change during or following finalization of FDA's LDTs framework.

- *BRCA testing for risk assessment or in chemotherapy selection:* Women who have mutations in the *BRCA* gene are at sharply increased risk for breast and ovarian cancer. Thus, these tests are used in asymptomatic individuals to assess their risk of developing a future cancer and can aid women in the decision to have risk-reducing surgeries (such as a mastectomy or a salpingo-oophorectomy to remove the ovaries and fallopian tubes). *BRCA* testing is also used in women with breast or ovarian cancer to determine if they are eligible for a class of chemotherapeutic drugs called PARP inhibitors. Given the high risk decisions that are influenced by *BRCA* testing, we believe these tests should be classified as the highest risk tests and undergo priority review by the FDA. Prior to and during review, these tests will remain on the market and be available to patients and their providers.

Conclusion

The Alliance is united with many other advocacy groups, including those within the larger cancer patient and research community[7,8,9], in support of increased regulation and oversight of LDTs. We believe that

[7] November 21, 2012. Cancer Leadership Council letter to OMB. "CLC Urges Release of Draft Guidance on Laboratory Developed Tests." Available at: www.cancerleadership.org/policy/fda/text/121121t.html

[8] August 4, 2014. Christopher W. Hansen, President of the American Cancer Society Cancer Action Network. "FDA Regulation of Laboratory Developed Tests Will Improve Patient Safety." Available at: www.acscan.og/content/media-center/fda-regulation-of-laboratory-developed-tests-will-improve-patient-safety-2/

[9] September 9, 2014. "Reliable and Effective Diagnostics are Keys to Accelerating Personalized Cancer Care: A Policy Statement from the American Association for Cancer Research Policy." Available at: www.clincancerres.aacrjournals.org/content/early/2014/09/05/1078-0432.CCR-14-2295

the regulatory paradigm laid out by the FDA in its draft framework would provide robust patient protections and ensure that all molecular diagnostics – whether they are LDTs or distributed as kits by a manufacturer – are valid, reliable, safe and effective. We look forward to a robust discussion with the Committee and other stakeholders during the open comment period for FDA's draft guidance.

December 10, 2014

Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Sir or Madam:

As leading organizations representing the interests of patients, providers and other stakeholders in a wide range of disease areas, we are writing to commend the release of the draft guidance on the framework for regulatory oversight of laboratory developed tests (LDTs). The draft guidance represents a critical turning point in the development of advanced diagnostics and it is essential that the FDA move forward with a transparent and open comment period to ensure appropriate and efficient oversight of safe and effective diagnostics.

Diagnostic tests play an important role in the advancement of patient care, from detection of new emerging infectious diseases and identification of effective antibiotics to the advanced molecular diagnostics that are accelerating the development and application of personalized medicine. These tests represent one of the most effective areas of healthcare, efficiently providing a wealth of information that is used by doctors and patients to make critical decisions at every stage of care. Especially because of the continuing development of new molecular diagnostics, there is a growing reliance on these tests by doctors and patients to make diagnosis and treatment decisions. This growing reliance, however, means that the risks to patients are much higher if these tests do not perform as expected. False results, or missed or incorrect diagnoses, could mean that patients either will not receive the therapy they need, or will be subject to the adverse effects and costs of a therapy that will not work for them.

Currently, a diagnostic test produced by a manufacturer and sold to a laboratory must first obtain pre-market clearance or approval from FDA to support the safety and effectiveness of the test. These tests are also subject to comprehensive quality system requirements from design through distribution, as well as post-market oversight that includes mandatory adverse event reporting and FDA's recall authority.

Laboratories that develop, manufacture and use a similar test, however, do not obtain pre-market approval for tests offered and are also not subject to a post-market surveillance system. Yet these LDTs are widely used as interchangeable with FDA-approved or cleared diagnostics, with patients or even doctors often unaware of the regulatory status of the test being used to make critical treatment decisions.

Laboratories are subject to regulatory oversight under the Clinical Laboratory Improvement Amendments (CLIA), which is run by the Centers for Medicare and Medicaid (CMS). CLIA ensures that labs are following good lab practices including the employment of credentialed lab personnel and testing procedures set out laboratory quality standards. Unlike FDA oversight of diagnostics, CLIA **does not** regulate the safety and effectiveness of diagnostic tests, **does not** require pre-market review or a regulatory review process for tests, **does not** require demonstration of clinical validity, **does not** require independent review of clinical claims, **does**

not require adverse event reporting system for tests, and **does not** have a process for corrections or recalls.

CMS, the agency that oversees CLIA, released a FAQ in October 2013 highlighting the differences between CMS review of LDTs and FDA review of IVDs. In particular, CMS itself notes:

- "[T]he regulatory schemes of the two agencies are different in focus, scope, and purpose…"
- "CLIA and its implementing regulations do not affect FDA's authority under the FDCA to regulate LDTs or other devices used by laboratories."
- "LDTs … have not undergone FDA premarket review, which assures both the analytical validity (e.g., analytical specificity and sensitivity, accuracy and precision) and clinical validity of IVDs."
- "The FDA's processes also assess clinical validity…as part of the review that is focused on the safety and effectiveness of the test system."

Congress gave FDA authority over all in vitro diagnostic (IVD) tests, including LDTs, in the Medical Device Amendments of 1976. FDA chose to exercise enforcement discretion of LDTs because, at the time, these tests were generally low-risk tests, or used for rare conditions for which adequate validation would be difficult, if not impossible. Over 30 years later, LDTs are now being used to assess high-risk and relatively common diseases and conditions and to inform critical treatment decisions. As a result, there are significant and well recognized gaps in the current regulatory environment for LDTs, including a pre-market review process to ensure safety and effectiveness of tests and a post-market surveillance system that is designed to assure quality and patient safety throughout the product lifecycle.

It has become clear that the historical paradigm that led to enforcement discretion is no longer valid. Patients and other stakeholders have recognized the growing use of LDTs and the likelihood that doctors and patients may not know whether the test they are relying on for course of treatment has been vetted for safety and effectiveness. A modernized regulatory process that encourages timely and efficient oversight of all diagnostics, regardless of where they are developed, is needed to promote innovation and ensure patient safety.

The draft guidance therefore represents a significant step forward in addressing this regulatory gap and resolving the uncertainty surrounding this critical area of medicine by reaffirming FDA's oversight of diagnostics. As proposed, the risk-based approach would allow the agency to focus its resources while supporting both innovation and the public health. This approach allows the agency to implement a flexible, efficient regulatory approach for all diagnostics. In doing so, it balances the need for access to safe and effective tests from low-risk, small population tests, tests for unmet needs, to high-risk tests used for broad populations or as the sole determinant of a treatment decision.

The draft guidance details agency thinking into the types of tests that would be regulated and how they would be regulated. We are encouraged by this critical first step. The open comment period is an important next step. We urge the FDA to engage all stakeholders in a public and transparent process as you work toward a final guidance document in a timely manner.

Sincerely,

AIDS Institute
Alliance for Aging Research
American Association for Cancer Research
American Cancer Society Cancer Action Network
American Heart Association
American Society for Clinical Oncology
Colon Cancer Alliance
Facing our Risk of Cancer Empowered (FORCE)
Melanoma Research Alliance
National Down Syndrome Society
Ovarian Cancer National Alliance
United Spinal Association
ZERO - The End of Prostate Cancer

Ovarian Cancer National Alliance

Statement for the Record

U.S. House Energy & Commerce Committee

Subcommittee on Health

Hearing: "21st Century Cures: Examining the Regulation of Laboratory Developed Tests"

September 9, 2014

The Ovarian Cancer National Alliance (hereafter the Alliance) would like to thank Chairman Pitts, Ranking Member Pallone and Members of the Subcommittee for the opportunity to comment upon the recent hearing regarding the regulation of laboratory developed tests (LDTs). The Ovarian Cancer National Alliance is a powerful voice for everyone touched by ovarian cancer. We connect survivors, women at risk, caregivers and health providers with the information and resources they need. We advocate at a national level for greater investment in federal research to support the development of an early detection test, improved health care practices and life-saving treatments.

During the hearing, we were pleased to hear so many Members of the Subcommittee call for stronger oversight of LDTs, even if there was disagreement on which agency should carry out that oversight. Ensuring that LDTs are valid, reliable, safe and effective is of critical importance to the ovarian cancer community, as we have experienced firsthand the harmful repercussions of an unregulated LDT. As we also heard many Members ask for examples of harmful LDTs, we submit this letter to detail our community's experience with OvaSure, a harmful LDT pulled from the market in 2008.

OvaSure – A Case Study Highlighting the Need for LDT Regulation

Ovarian cancer is a highly deadly disease, taking the lives of nearly 14,000 women in the United States each year. A full quarter of women diagnosed with ovarian cancer will survive less than one year, and over half won't live five years past diagnosis. These grim statistics are due to the fact that there is no early detection test for ovarian cancer – though the need is obviously great. Most cases of ovarian

cancer are caught only after the disease is in its most advanced stages and difficult to effectively treat. However, when the disease is caught early, it can be treated effectively through surgery and chemotherapy.

It is against this backdrop that, in 2008, Labcorp began marketing an LDT called OvaSure as an early detection test for ovarian cancer. The test had been developed by Dr. Gil Mor at Yale University and was quickly commercialized by the testing company, before it had been sufficiently validated.

Almost immediately upon commercialization, the Food and Drug Administration (FDA)[1] and the Society of Gynecologic Oncology[2,3] stated that they did not believe the test had been validated enough for routine clinical use. Furthermore, it was reported that women using the test had experienced false positives[4] and false negatives[5] – leading otherwise healthy women to unnecessarily have their ovaries removed and leaving some women with a false sense of security after missing their cancer diagnosis. Both of these outcomes put women at exceptional and unnecessary risk.

The OvaSure test was eventually pulled after four months on the market[6]. Since laboratories offering LDTs are not required under the Clinical Laboratory Improvements Act (CLIA) to report adverse events, we do not know precisely how many women were harmed by the OvaSure test, but we do know that the test should have never been on the market to begin with.

FDA Regulation of LDTs Will Prevent the Next OvaSure

The Alliance applauds FDA's recent steps towards ensuring that all molecular diagnostic and genetic tests are validated to certify that they are reliable, safe and effective. We welcome the development and use of tests that can help guide treatment for women with and at risk of developing ovarian cancer, but we must first have confidence that these tests are valid. FDA regulation of LDTs will ensure that.

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[1] August 7, 2008. OvaSure Manufacturer Letter from the Food and Drug Administration to LabCorp. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm125130.htm

[2] On April 4, 2012, the Society of Gynecologic Oncologists changed its name to the Society of Gynecologic Oncology. All references to the organization in this letter will use its current name.

[3] July 2, 2008. Society of Gynecologic Oncology Statement Regarding OvaSure. Available at: https://www.sgo.org/wp-content/uploads/2012/09/Statement-On-Ovasure.pdf

[4] August 25, 2008. Andrew Pollack. "Cancer Test for Women Raises Hope, and Concern." New York Times. Available at: http://www.nytimes.com/2008/08/26/health/26ovar.html?pagewanted=1&_r=0

[5] March 23, 2011. Lizzie Buchen. "Cancer: Missing the mark." Nature. Available at: http://www.nature.com/news/2011/110323/full/471428a.html

[6] October 24, 2008. Andrew Pollack. "Sales of Test for Ovarian Cancer Halted." New York Times. Available at: http://www.nytimes.com/2008/10/25/business/25cancer.html

We deeply appreciate and support several facets of FDA's proposed regulatory framework for LDTs:

- *Risk Based Framework:* FDA proposes a phased-in, risk-based framework to regulate LDTs. In short, FDA will classify LDTs by their risk level and phase in review of those tests by prioritizing the highest risk tests. Tests will be classified as high risk if they are used as the basis of any high risk medical decision, such as picking a chemotherapy, diagnosing a disease in asymptomatic individuals and evaluating blood and blood products for use in humans. This will include any companion diagnostic tests or an LDT that mimics a companion diagnostic currently on the market. It is likely that many of the tests relevant to the ovarian cancer community will count as class III tests (e.g. BRCA testing for chemotherapy selection or prophylactic surgery, early detection tests and tests to monitor disease recurrence). Under the risk based framework, tests currently on the market will remain on the market while they are awaiting review, though all new tests must be reviewed prior to being offered. Had this framework been in effect in 2008, OvaSure would have been required to undergo FDA review for analytical and clinical validity prior to being put on the market. OvaSure's substantial flaws would have been identified through this process and it would have been identified through this process, and patients and providers would have been spared the adverse consequences of an inaccurate, unreliable test.

- *Adverse Event Reporting:* Within six months of the finalization of FDA's guidance, laboratories will be required to report all adverse events resulting from the use of their tests to the FDA. Using the example of OvaSure, events such as the misdiagnosis of ovarian cancer in healthy women (false positives) or missing ovarian cancer recurrence (false negatives) would be reported to the FDA. Had this oversight been in place in 2008, we would have an accurate count of the number of women harmed by the OvaSure test.

Furthermore, we believe that FDA's action to end enforcement discretion with regard to LDTs will provide clarity and peace of mind to patients, providers and payers. As LDTs are increasingly being used to guide complex medical treatment decisions, it is critical that when patients and their doctors use such a test, they know the results can be trusted. Payers will also be able to better assess the benefit and value of a test, allowing them to decide if a test should be covered, for which patients, and at what reimbursement rate.

The Impact of FDA Regulation of LDTs on Ovarian Cancer Patients

Under FDA's proposed framework to regulate LDTs, ovarian cancer patients will continue to have access to all the diagnostics currently used in their care. There are currently two main classes of diagnostics being used by ovarian cancer patients and their providers and we will summarize each below:

- *Tests to diagnose suspected ovarian cancer and monitor disease recurrence:* There are currently three molecular diagnostic tests on the market used to either diagnose ovarian cancer when it is suspected or to monitor disease recurrence in survivors. These three tests – CA-125, HE-4 and OVA-1 – have all gone through the premarket review process and been cleared by the FDA. Their status will not change during or following finalization of FDA's LDTs framework.

- *BRCA testing for risk assessment or in chemotherapy selection:* Women who have mutations in the *BRCA* gene are at sharply increased risk for breast and ovarian cancer. Thus, these tests are used in asymptomatic individuals to assess their risk of developing a future cancer and can aid women in the decision to have risk-reducing surgeries (such as a mastectomy or a salpingo-oophorectomy to remove the ovaries and fallopian tubes). *BRCA* testing is also used in women with breast or ovarian cancer to determine if they are eligible for a class of chemotherapeutic drugs called PARP inhibitors. Given the high risk decisions that are influenced by *BRCA* testing, we believe these tests should be classified as the highest risk tests and undergo priority review by the FDA. Prior to and during review, these tests will remain on the market and be available to patients and their providers.

Conclusion

The Alliance is united with many other advocacy groups, including those within the larger cancer patient and research community[7,8,9], in support of increased regulation and oversight of LDTs. We believe that

[7] November 21, 2012. Cancer Leadership Council letter to OMB. "CLC Urges Release of Draft Guidance on Laboratory Developed Tests." Available at: www.cancerleadership.org/policy/fda/text/121121t.html

[8] August 4, 2014. Christopher W. Hansen, President of the American Cancer Society Cancer Action Network. "FDA Regulation of Laboratory Developed Tests Will Improve Patient Safety." Available at: www.acscan.og/content/media-center/fda-regulation-of-laboratory-developed-tests-will-improve-patient-safety-2/

[9] September 9, 2014. "Reliable and Effective Diagnostics are Keys to Accelerating Personalized Cancer Care: A Policy Statement from the American Association for Cancer Research Policy." Available at: www.clincancerres.aacrjournals.org/content/early/2014/09/05/1078-0432.CCR-14-2295

the regulatory paradigm laid out by the FDA in its draft framework would provide robust patient protections and ensure that all molecular diagnostics – whether they are LDTs or distributed as kits by a manufacturer – are valid, reliable, safe and effective. We look forward to a robust discussion with the Committee and other stakeholders during the open comment period for FDA's draft guidance.

January 5, 2015

The Honorable Fred Upton
Chairman
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Diana DeGette
2368 Rayburn House Office Building
Washington, D.C. 20515

Sent via e-mail: Cures@mail.house.gov

Re: Request for Information Regarding Laboratory Developed Tests

Chairman Upton, Representative DeGette:

O[redacted]r Action Network, I thank you for the opportunity to provide input to the 21st *Century Cures Initiative* request for input on the issue of FDA's recent proposal on laboratory developed tests (LDTs).

Pancreatic cancer is one of our nation's deadliest cancers, with a five-year relative survival rate of just 6 percent. Currently, there are no early detection methods or effective treatments. The Pancreatic Cancer Action Network's goal is to double survival by 2020. One of the ways that we are working to achieve this bold goal is our Know Your Tumor (KYT) initiative in which we are offering pancreatic cancer patients access to molecular information specific for their tumor. Please see the attached fact sheet for more information on the initiative.

Molecular profiling offers pancreatic cancer patients the opportunity to identify specific gene alterations in their tumor and corresponding treatments that have been approved for the same molecular alterations in other cancer types. Given the scarcity of pancreatic cancer treatments this is an exciting approach for the field and presents a great opportunity for an area that has such unmet need.

There is no question that genomic profiling will be a key component of pancreatic cancer treatment moving forward. We are generally supportive of FDA's draft guidance on LDTs, but are concerned that it does not specifically address the review of gene panels.

Access to pancreatic cancer tissue is difficult to obtain and therefore very limited. Because the pancreas is located deep in the body behind the abdomen, biopsy tissue is scarce and significant tissue is only available as a result of surgery. However, only 15 percent of

pancreatic adenocarcinoma patients are eligible for surgery. **Therefore, we believe that it is critical that any future guidance that is developed regarding FDA's oversight of gene panels must ensure that limited tissue samples can be used in the most effective way. Specifically, we believe that it is important that pancreatic cancer patients are allowed to continue to use assays that cover the largest number of molecular alterations possible, irrespective of whether tests have been approved for individual variations.**

I thank you for the opportunity to submit comments. If you have questions or need more information, please contact me at 202.742.6776/mgdon@pancan.org.

Sincerely,

[redacted]

Megan Gordon Don
Vice President, Government Affairs & Advocacy

Attachment: Fact Sheet on Know Your Tumor

PANCREATIC CANCER ACTION NETWORK SM

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Government Affairs and Advocacy
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PMC
PERSONALIZED
MEDICINE COALITION

January 5, 2015

The Honorable Fred Upton (R-MI)
Chairman
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Diana DeGette (D-CO)
Member
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, D.C. 20515

Sent via email: Cures@mail.house.gov

Re: Request for Information Regarding *21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests*

Dear Chairman Upton and Representative DeGette:

Thank you for engaging the community on the 21st Century Cures initiative. Your focus on accelerating the pace of medical breakthroughs is generating ideas that could greatly improve the quality of patient care in the United States, including proposals to promote personalized medicine, which is on the cutting edge of biomedical innovation.

The Personalized Medicine Coalition (PMC), representing innovators, scientists, patients, providers and payers, promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health system. We thank the Committee for including PMC in its work so far and for this opportunity to engage.

As you know, personalized medicine is an emerging field that uses diagnostic tools to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will be best for each patient. By combining this information with an individual's medical records and circumstances, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans. The goal is to provide the right treatment to the right patient at the right time.

In *21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests,* a list of questions is posed along with a request for answers to them. We understand that the Committee has been working on an extensive legislative package to advance health care innovation generally. Although the request for information covers issues related to all diagnostic tests, PMC's comments focus on personalized medicine diagnostics in particular. Our answers are also heavily focused on FDA's recent notice to Congress and subsequent publication of two draft documents related to the regulation of laboratory developed tests, *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs),* and *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs).*

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PMC's answers are designed to suggest policy improvements that will help personalized medicine advance. Many of PMC's members will present their own responses to the Committee, and will actively advocate for those positions. To support the work of our member organizations we therefore note the following disclaimer: nothing in this letter is intended to impact adversely in any way the ability of individual PMC members, alone or in combination, to pursue separate comments, litigation, or other remedies with respect to FDA's proposed regulatory framework for LDTs, responses to the Committee's questions, or related issues.

We greatly appreciate the thoughtful and important questions that the Committee has raised, but given the short timeline, we have elected at this time to address only some of the Committee's questions. For clarity, we have maintained the original numbering and restated the entire question for each of the questions we are addressing.

3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?

PMC supports a risk-based approach to diagnostic test regulation. Risks posed by diagnostic tests are very different from a therapeutic medical device. Traditional medical device classification, therefore, is not entirely appropriate for diagnostic tests. FDA plans to develop a risk-classification system for LDTs. A new risk-classification for diagnostics, developed with significant stakeholder input, that provides for a more flexible balance between the relative risks posed by diagnostic tests and the potential benefit of the information that tests provide would be most appropriate and would logically fit within FDA's activities designed to promote personalized medicine and the regulatory science behind it.

As acknowledged above, FDA has issued a draft framework for the regulation of LDTs that is risk-based and tiered so that the highest risk tests must comply with FDA regulatory structure first. However, the draft framework proposes to apply the therapeutic medical device risk classifications to diagnostics initially as the classification system for LDTs is developed. The FDA currently intends to release its risk-classification draft guidance document 24 months after the finalization of the current guidance documents. The risk and classification piece is of tremendous importance to any potential regulatory oversight. PMC thinks it is vital that the concepts of risk and classification be resolved before the framework is finalized. This will substantially alleviate much of the uncertainty that currently exists around the FDA's proposed draft guidance. We request that FDA issue a risk-classification draft guidance document along with a second draft of the framework so that the public can consider and comment on both together.

4. The current pre-market review standards that apply to in vitro diagnostics use the same terminology of safety and effectiveness that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?

Pre-market review standards should be risk-based. Evaluation of traditional medical device concepts like safety and effectiveness should likewise be risk-based and might not be completely appropriate for all diagnostic tests or LDTs. Diagnostic tests provide information to a treating physician, who makes decisions based on test information, clinical information, disease state, prior diagnosis and many other patient-specific factors. Therefore, the risk profile for a diagnostic differs substantially from that of a therapeutic medical device, and the application of existing pre-market standards for safety and effectiveness may have to be modernized so that they are more appropriate when applied to diagnostic test kits and LDTs.

5. Are there areas where the balance between pre-market reviews versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

Shifting the focus of diagnostic regulation by some degree from pre-market review to post-market controls should be considered for the vast majority of LDTs and should also be considered as an appropriate path for the regulation of LDTs. Personalized medicine diagnostic tests often enter the market and evolve from or reflect scientific advances and constantly evolving clinical research. Therefore, this focus shift from pre-market review to post-market control has two distinct benefits. First, it allows tests to enter the market in response to medical need. Second, it allows tests to develop along with the science and advances in clinical research.

FDA has, for some devices and diagnostics, used an expedited pre-market approval (PMA) process, which has been welcomed by innovators and has been a great success. Significant expansion of the expedited PMA process would be welcome as changes to the current FDA system for test regulation are considered.

We are concerned that the current medical device statute is too inflexible to allow FDA to adjust or modify the current standards for clearance or approval to allow personalized medicine tests or changes to them based on rapidly evolving clinical information to reach patients. To the extent that the FDA does not have the flexibility necessary to make this shift under current statutory authority, Congressional action might be necessary. Stakeholders would likely support a legal remedy that enables the agency greater flexibility in the de novo application process.

6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?

We, too, are concerned about how FDA proposes to handle test modifications by clinical laboratories. For example, sometimes clinical laboratories must alter a test to improve its performance characteristics by making small technical adjustments that do not change the intended use of the test. Furthermore, as mentioned above, personalized medicine diagnostic tests often evolve rapidly in response to scientific advances. Modifications that do not change the intended use, but provide additional information that may enhance or improve treatment decision-making should be allowed by FDA in a streamlined manner. Finally, personalized medicine is already in the process of moving from a one-marker, one-test field to one in which hundreds and perhaps soon thousands of bits of information are discovered from a test. While the test might not change, the clinically actionable information will change over time. It is not clear that under the current statute FDA has the ability to address these near-future changes regarding actionable information in the least burdensome manner without impacting patient access. A flexible, modular system for approving modifications would help personalized medicine maintain its current pace alongside clinical and scientific advancements.

7. We have heard a lot about the practice of medicine and its relationship with medical product "labeling." What should comprise "labeling" for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?

Within the FDA draft framework for LDT regulation, it is unclear how FDA would handle redundancies and conflicts with the CLIA program, under which clinical laboratories are now regulated, including labeling requirements. Below, we explain two examples of why FDA medical device labeling does not necessarily fit LDTs, and make suggestions for how labeling issues for LDTs might be resolved.

Because the rules for device labeling conflict with the CLIA program, FDA should provide a comprehensive explanation of how it would apply device-labeling requirements to LDTs. A laboratory should be permitted to fulfill any mandatory labeling requirements solely through its online directory of services. Section 502(f) of the

FDCA (21 U.S.C. § 352 (f)(2)) authorizes the use of electronic labeling in lieu of paper-based labeling under certain circumstances. This provision states, in part:

> *[r]equired labeling for prescription devices intended for use in health care facilities or by a health care professional and required labeling for in vitro diagnostic devices intended for use by health care professionals or in blood establishments may be made available solely by electronic means, provided that the labeling complies with all applicable requirements of law, and that the manufacturer affords such users the opportunity to request the labeling in paper form, and after such request, promptly provides the requested information without additional cost.*

FDA should not require clinical laboratories to maintain labels or labeling in formats required for distributed/shipped products.

Furthermore, current FDA device labeling regulations will have negative consequences on the practice of medicine if applied to LDTs. Laboratory physicians, such as pathologists, advise treating physicians about available tests, test results, and possible treatment decisions that follow testing as part of the practice of medicine and based on their medical training and expertise. Current device regulation will hamper this aspect of the practice of medicine, an aspect upon which personalized medicine depends, because of potential off-label concerns. Briefly, pathologists or laboratory physicians routinely discuss options, which appear to modify FDA-approved or cleared devices. When physicians are treated as manufacturers, rather than medical professionals, such off-label uses cannot be discussed. When a test has been "labeled" for one use but is appropriate for another use, a manufacturer is prohibited from revealing that use, but physicians are permitted to discuss off-label uses. We are concerned that the agency intends for such other uses to be treated as off-label until "labeling" requirements are met again based on the new intended use. Thus, clarification is required regarding the extent to which the agency intends for this prohibition to apply to physicians who identify alternative uses that could require changes to labels. We suggest that the agency create a carve-out for off-label promotion for LDTs, so that laboratory physicians can discharge their duty to advise treating physicians seeking advice on relevant testing options. Laboratory-based physicians have both an ethical and legal obligation to serve as a resource to treating physicians on the most appropriate testing methods based on patient medical needs.

8. The Section 1143 guidance documents raise important questions about the relationship between the FFDCA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA's quality systems regulations compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?

PMC notes that many laboratories have concerns about the potential for duplication between the regulatory requirements that laboratories are subject to under CLIA and new requirements that would be imposed by the FDA's proposed framework. Duplicative regulations represent an unnecessary burden and cost for laboratories and the federal government. We are further concerned that FDA may move to finalize the proposed framework before outlining how these duplicative requirements will be streamlined.

FDA should be directed to harmonize its requirements with those already in existence under CLIA, and only impose regulatory requirements where the existing CLIA requirements are insufficient to achieve a specific regulatory goal. Particularly in the area of QSR, PMC notes substantial overlap in the regulatory requirements under FDA medical device regulation in 21 CFR §820 and the existing regulations under CLIA in 42 CFR §493 in relation to quality system requirements, design controls, document controls, purchasing controls, production and process controls, acceptance activities, nonconforming products, corrective and preventative actions, and records. It is critically important that FDA be required to identify the least burdensome approach to QSR, deferring to CLIA where regulatory goals overlap and are adequately met.

Likewise, CMS and FDA should be directed to issue a joint draft guidance document in conjunction with a public process for comment consideration from all stakeholders. We propose that draft guidance documents should clearly state that the CLIA program will suffice where there is overlap and that FDA will start where CLIA ends. Conflicts between the two programs should be fully resolved before the framework is finalized, since it is our understanding that before a PMA is filed, a quality system inspection must be completed. Therefore, requirements should be fully articulated, with opportunity for stakeholder comments first, so that laboratories can develop appropriate internal systems.

9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g. Ebola)?

PMC has long argued that the United States needs a creative, dynamic and flexible diagnostic test industry to support the future of health care and protect the public health from emerging threats. For optimal diagnostic industry capability, we must ensure that regulatory systems are designed in a way that protects patient safety in a flexible manner responsive to both emerging medical needs and the evolving science of personalized medicine.

Conclusion

Thank you again for recognizing and tackling this important set of issues. PMC appreciates the opportunity to provide comments now and in the future as the Committee continues its work to identify the appropriate legislative balance between regulation, innovation and access to personalized medicine diagnostic tests.

We would like to take this opportunity to conclude with a request. As you know, FDA has issued a draft framework for the regulation of LDTs and an accompanying notification process. We referenced the framework many times in the letter above. During public meetings, FDA staff members have stated that FDA intends to issue a second draft of the framework only if changes are significant.

PMC has requested additional information on risk classification, harmonization between the CLIA program and FDA inspections, technical test modifications and labeling issues.

Alone, each of these issues is significant; yet together it is clear that, at the very least, a second draft of the framework should be issued together with draft guidance documents clarifying the missing pieces for the review and public engagement process to be complete. We request that FDA resolve outstanding issues, publish draft guidance documents on risk and CLIA-FDA harmonization, open a docket for the collection of public feedback and engage in a series of public engagement activities such as a webinar and public meeting.

We have many other requests of and suggestions for the agency, but this one is most critical. If you have any questions or require more information, please contact Amy Miller by phone at 202-589-1769 or email at amiller@personalizedmedicinecoalition.org.

Sincerely yours,

Edward Abrahams, Ph.D.
President

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January 9, 2015

The Honorable Fred Upton, Chairman
House Committee on Energy & Commerce
2125 Rayburn House Office Building
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The Honorable Diana DeGette
House Committee on Energy & Commerce
2268 Rayburn House Office Building
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RE: University of California, San Francisco (UCSF) Comments in Response to "21st Century Cures."

Dear Chairman Upton and Representative DeGette:

On behalf of the University of California, San Francisco (UCSF), the nation's leading university exclusively focused on health, we appreciate this opportunity to provide recommendations in response to the Committee's landmark *21st Century Cures* initiative.

UCSF applauds your commitment to identify and address gaps and challenges in the current federal research enterprise that hinder scientific discovery and the process of translating those discoveries into cures and treatments for patients.

As the nation's top public recipient of funding from the National Institutes of Health (NIH) and the birthplace of biotechnology, UCSF has long served as a national model for creating a successful ecosystem of innovation that has an impact on both research and patient care. UCSF has a university-wide commitment to Precision Medicine, a concept grounded in the dedication of UCSF's clinical, basic and social and behavioral researchers to integrate their efforts and discoveries to directly benefit patients and to reveal new research opportunities.

Supporting the goals of the *21st Century Cures* initiative and reflecting the breadth of work and expertise at UCSF, we offer seven key recommendations: 1) support a sustained NIH funding model, 2) create a federal Precision Medicine Initiative, 3) expand FDA extramural research, 4) expand innovative regulatory pathways, 5) grow the NSF Innovation Corps (I-Corps) entrepreneurship education program, 6) promote interagency research and cooperation, and 7) support Electronic Health Record data sharing for research.

Sustained NIH Funding

Recognizing the immense federal budget challenges our nation faces and the constraints of the Energy & Commerce Committee's jurisdiction, UCSF urges the Committee to include a strategy for providing NIH with a stable and predictable funding model. For nearly seventy years, the nation's research investment through the NIH has improved our understanding of the causes of disease, thereby increasing life expectancy and

enhancing the health of Americans. Some of the most profound and impactful work has been through NIH support of research at UCSF, as recognized by five Nobel Prizes, twelve Lasker Awards, four Shaw Prizes, forty-nine National Academy of Sciences members and ninety-two Institute of Medicine members. NIH funding has helped UCSF become the second largest employer in San Francisco and the fifth largest in the Bay Area, contributing more than $6 billion a year to the regional economy. This funding also has led to the spinoff of biomedical research companies, including the first, Genentech, and more than ninety others, creating economic benefits that extend regionally, nationally and internationally.

The willingness of researchers to undertake bold, high impact investigations depends on their confidence in the federal commitment to funding. "Feast-famine" cycles are the most damaging. For example, the NIH budget doubled between 1998 and 2003, but since then, the spending power of the NIH budget has declined by nearly 25%.

> ***Legislative Proposal:*** *UCSF has not singled out for endorsement any particular legislative proposal for increased and sustained NIH funding that has been introduced or appears likely to be introduced in Congress, but there are several principles that UCSF supports in any model that the Committee considers: (a) high priority to return NIH budget spending power to 2003 levels as soon as possible; (b) a rolling three to five year budget commitment in support of NIH research; (c) linkage of a "base" NIH budget to Biomedical Research and Development Price Index (BRDPI), with subsequent budget consideration beginning from that base.*

Precision Medicine – Create a Cross-Agency Initiative

In late 2011, a National Academy of Sciences committee endorsed a broad operating concept, "Precision Medicine," as the best means to organize and integrate biological and biomedical research, and to advance understanding of the mechanisms, diagnosis, treatment, cure, and prevention of all forms of disease.

At present, the levels of integration, coordination and dissemination of information collected in the course of basic, clinical and social/behavioral research are relatively poor; thus, we are not optimizing all available information relevant to health and disease. Precision Medicine would represent a single computational platform on which all research findings about normal and aberrant biological processes derived from experimental organisms like mice, worms, flies and yeast, would be combined with all studies of well and diseased people. This would include clinical, laboratory and imaging information in individual electronic medical records and, increasingly, knowledge derived from the genome and its expression, as well as data gathered and reported by wearable electronic devices.

Achieving Precision Medicine will require joint cooperative efforts across all stakeholder sectors: academia, government, industry and nonprofit agencies, and the public at large. The goals are challenging, but the four major outcomes merit the effort: 1) a research ecosystem that for the first time integrates and makes full use of discoveries in basic, clinical and social/behavioral sciences, 2) health and health care tailored precisely to each individual, 3) greater worker productivity, with a higher quality of life, and 4) reduced health care costs due to improved prevention, early precise diagnosis, better control of chronic disease, and avoidance of unnecessary tests and ineffective therapies.

Legislative Proposal: *UCSF recommends a legislative provision modeled on the 21st Century Nanotechnology Research and Development Act of 2003 (Public Law 108-153), to set up a coordination office and evaluation process to oversee a sustained trans-agency, trans-sector effort to establish Program Component Areas to achieve Precision Medicine, including addressing regulatory and ethical issues of patient data privacy and security.*

FDA Research – Expand Centers of Excellence in Regulatory Science and Innovation

Rapid advances in innovative science are bringing fundamental changes to the way FDA-regulated products are developed, evaluated, manufactured, and used. Evolving areas of science, like cell therapy and nanotechnology, are promising novel approaches to improving our health while demanding new ways to evaluate the safety and effectiveness of these products. The ever-present challenge for the FDA to keep pace with changes and meet the needs of academia, industry and consumers is expanding rapidly.

In 2011, the FDA established two Centers of Excellence in Regulatory Science and Innovation (CERSIs), and in 2014 expanded by funding two additional centers, including one at UCSF. CERSIs are based in academia and charged to work with both FDA and private industry to advance the concept and field of regulatory science, which encompasses the training and research necessary to shape a science-based decision-making process that will enable FDA to initiate new and more rational regulatory pathways, to form new avenues that both employ and evaluate novel, even revolutionary new technologies, and expand the capacity and efficiency of safety and efficacy evaluations as well as monitoring of candidate and licensed products.

Legislative Proposal: *UCSF recommends that the Committee authorize support for a network of 10-12 CERSIs, including the current four, which represents the geographical diversity of the United States and encompasses the range of expertise required for medical product review and evaluation (e.g., drugs, devices, biologics, digital health, pre-clinical evaluation, clinical trials, computation and large databases, laboratory-based, population based, and manufacturing). CERSI research and education programs should be mission-based in order to define and approach new scientific horizons and to address the unmet needs of the FDA and industry. Each CERSI costs approximately $1.1 million annually.*

FDA – Expand Innovation Pathway Program

In 2012, the FDA created an Innovation Pathway pilot program, which establishes close contact between the federal agency and device developers early in the development process to identify and address potential scientific and regulatory hurdles and to build a roadmap for project approval. The goal is to improve the projects' overall chance of success, while reducing the time and cost of FDA review and maintaining safety. At UCSF, developers of an implantable bio-artificial kidney have been participating in Innovation Pathway 2.0. The project has the potential to save the lives of millions of Americans facing end-stage renal disease, one of the most costly diseases in the United States. Innovation 2.0 has helped speed the development process for the groundbreaking technology, while making the project more attractive to investors.

Legislative Proposal*: UCSF recommends incentivizing FDA to use the authority that exists under current law to broaden Innovation Pathway regulatory programs to meet critical health needs.*

Expand I-Corps

One of the challenges of the gap between academia, industry and moving scientific discovery along the path to commercialization is that the majority of scientists are not trained in business or entrepreneurship. I-Corps is a successful NSF program that could be expanded to other federal research agencies to address that gap.

NSF and NIH recently collaborated to create the NIH Innovations Corps (I-Corps) Team Training Pilot Program. The pilot is modeled after the NSF I-Corps program that funds several hubs across the country, including UCSF, which offer a targeted curriculum that teaches grantees to identify valuable product opportunities that can emerge from academic research and that offers entrepreneurship training to participants.

The pilot program at NIH targets projects supported by Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) awards and is designed to support training that will help project teams at NIH-funded small businesses learn the tools that will help overcome obstacles along the path of innovation and commercialization.

> ***Legislative Proposal:*** *UCSF recommends that the I-Corps program be extended permanently and expanded beyond its current scope to all NIH Institutes and make incorporation mandatory for all major research funding agencies that fund SBIR/STTR programs.*

Create Mechanisms to Promote Interagency Research and Cooperation

The U.S. federal government has long provided the world's most robust program of support for scientific research, recognizing in particular the essential role of public support for innovative, untargeted basic research—much of which takes place within our academic institutions. A clear demonstration of the enthusiasm of governmental support is the spectrum of federal agencies that help organize, and subsequently fund generously, programs for scientific research and training. For example, biomedical research is supported by well over twenty federal agencies. Unfortunately, this decentralized mode of government funding for research substantially complicates efforts to achieve transdisciplinary integration.

UCSF supports the recommendation made by the American Academy of Arts and Science (AAAS) in their 2013 report, "Arise II: Unleashing America's Research & Innovation Enterprise," that the federal government devise new programs and policies to incentivize inter-agency coordination of scientific research and development.

> ***Legislative proposal:*** *UCSF supports legislative recommendations put forth in Arise II: 1) require the National Science and Technology Council to establish a coordinating committee to focus on scientific research interagency coordination; 2) encourage funding agencies to set aside a fraction of their budgets for projects jointly funded by multiple agencies; 3) promote transdisciplinary research and training through interagency supported research and training grants; 4) stimulate agencies that do not traditionally fund projects involving both academic and private sector participants in the DARPA tradition to consider pilot programs that test this approach to better achieve certain mission goals. The National Network for Manufacturing Innovation is an example of an initiative that was launched using existing funds from federal agencies and will be sustained through coinvestments by industry partners, state and local agencies, foundations, and the federal government. See http://www.manufacturing.gov/*

Pilot Programs for EHR Data Sharing

Electronic health records (EHRs) are a valuable tool for clinical research. EHR data can be used to identify eligible patients for clinical trials, monitor adverse drug reactions, and follow patient outcomes. However, because EHRs are designed to meet clinical practice needs, investigators who want to use EHR data for research must overcome numerous challenges. These challenges include the need to integrate information technology (IT) systems designed to support research with EHRs, the use of different terminologies in research and EHRs, and regulatory and institutional requirements that complicate if not preclude EHR use for research.

Creating a pilot program for clinical research networks would allow researchers to identify and implement best practices to support teamwork, data sharing and validation studies across institutions. A private consortium, the Global Alliance for Genomics and Health (Global Alliance) is developing data sharing strategies to maximize the potential of genomic medicine by enabling comparisons across millions of human genome sequences. The Global Alliance has devised a "Framework for Data Sharing" to guide governance and research as well as a Genomics Application Programming Interface to allow for the interoperable exchange of data. The potential to leverage this expertise through collaboration is extremely promising. More information can be accessed on the alliance's website: http://www.ga4gh.com.5

> ***Legislative Proposal:*** *UCSF recommends that the Committee authorize the Office of the National Coordinator for Health Information and Technology, in partnership with NIH and CMS, to convene a working group to identify policy and technical solutions to address the privacy and security issues for the sharing of EHR data for research studies. Further, the Committee should authorize the creation of a pilot program to form clinical research networks that would develop policies and demonstrate best practices for EHR data sharing.*

Thank you again for your leadership on this important issue and your consideration of these recommendations. If you have questions or if UCSF can be of assistance to you, please contact: Keith R. Yamamoto, Vice Chancellor of Research, at keith.yamamoto@ucsf.edu or (415) 476-8445 or Paul Takayama, Assistant Vice Chancellor, Community & Government Relations, at paul.takayama@ucsf.edu or (415) 476-3523.

Sincerely,

[redacted]

Sam Hawgood, MBBS
Chancellor
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SH:pt